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Award Number:

W81XWH-05-1-0056

TITLE:

PC040130 - "Cancer Localization in the Prostate with F-18
Fluorocholine Positron Emission Tomography"

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REPORT DATE:

Submitted January 15, 2009 and covering dates December 20, 2007 to
December 19, 2008

TYPE OF REPORT:

Addendum to Final Report 2006 and Addendum Report 2007.

PREPARED FOR: U.S. Army Medical Research and Materiel Command
               Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: (Check one)

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REPORT DOCUMENTATION PAGE

Form Approved
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1. REPORT DATE *(DD-MM-YYYY)* 1-15-2009	2. REPORT TYPE Addendum	3. DATES COVERED *(From - To)* 12/20/2007 – 12/19/2008

4. TITLE AND SUBTITLE

Cancer Localization in the Prostate with F-18 Fluorocholine

Positron Emission Tomography

5a. CONTRACT NUMBER
  W81XWH-05-1-0056

5b. GRANT NUMBER
  PC040130

5c. PROGRAM ELEMENT NUMBER
CFDA 12.420

6. AUTHOR(S)
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5d. PROJECT NUMBER
PC040130 (PC04-NIA)

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

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8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
Congressionally Directed Medical Research Program – Prostate Cancer Research Program (continued on right)

U.S. Army Medical Research and Materiel Command
1077 Patchel St. (Bldg. 1077)
Fort Detrick, MD 21702-5024

10. SPONSOR/MONITOR'S ACRONYM(S)
CDMRP - PCRP
USAMRMC HSRRB

11. SPONSOR/MONITOR'S REPORT NUMBER(S) HSRRB
Log No. A-13151.a, A-13151.b

12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for Public Release; Distribution Unlimited.

13. SUPPLEMENTARY NOTES

14. ABSTRACT
   The project evaluated fluorine-18 (18F-) fluorocholine positron emission tomography (PET) as an imaging technique for delineating malignancy in the prostate gland. The technique measures tissue metabolism of fluorocholine, a substrate that is preferentially metabolized by cancer cells due to malignant over-expression of the choline transporter and choline kinase enzyme. Based on this measurement, it was proposed that cancerous tissue can be differentiated from benign tissue in the prostate. Project Scope: Men with prostate cancer undergoing radical prostatectomy surgery underwent pre-operative PET scanning to measure fluorocholine uptake in the prostate gland. Imaging results were compared to histopathologic analyses of the prostatectomy specimen to determine the accuracy of prostate cancer sextant localization based on measured fluorocholine uptake. Recruitment of human subjects for this project was completed in 2008. A final one-year no-cost extension for a period of 20 December 2008 to 19 December 2009 is requested in order to complete final immunohistochemical analysis (proliferation index assays) of prostate specimens at the Armed Forces Institute of Pathology. Two subsequent research projects have been initiated based on the results of the current project. One project is a collaboration to develop clinically relevant image analysis tools for measuring the kinetics of 18F-fluorocholine activity in the prostate gland using PET/CT. The second project is a clinical trial proposal to assess treatment responses using 18F-fluorocholine PET/CT in clinically advanced prostate cancer.

15. SUBJECT TERMS
Prostate Cancer, Localization, Positron Emission Tomography, Fluorocholine

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON Sandi Kwee, MD
a. REPORT U	**b. ABSTRACT** UU	**c. THIS PAGE** U	Annual Report	29	**19b. TELEPHONE NUMBER** *(include area code)* (808) 585-5466

Standard Form 298 (Rev. 8-98)
Prescribed by ANSI Std. Z39.18

2008 Addendum to Final Report
Project: W81XWH-05-1-0056

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INTRODUCTION

The objective of this project is to develop and evaluate fluorine-18 labeled fluorocholine (18F-fluorocholine) as an imaging agent for positron emission tomography (PET) detection of malignancy in anatomical sextants of the prostate gland. The rationale for evaluating fluorocholine as an oncologic tracer applicable to prostate cancer is based on observations of increased choline and fluorocholine metabolism in malignant prostate tissue relative to normal tissue. Information about tumor activity, location, and volume obtained with PET may have significant clinical value in guiding transrectal biopsy or in refining therapeutic approaches against organ-confined prostate cancer.

REPORT SUMMARY

This final report addendum covers work performed during a no-cost extension period from 20 December 2007 to 19 December 2008. Human subject recruitment was completed during this period and the study is now closed to further accrual. Twenty-five specimens have been received by the Armed Forces Institute of Pathology (AFIP) for histopathologic correlations with PET and PET/CT. Preliminary clinicopathologic-imaging correlation analysis has been completed with data from 24 subjects. The PI is planning a visit to AFIP in March 2009 to review final histopathologic data with AFIP personnel. Final study results will be available after completion of this visit.

Work on new projects has been initiated based on the results of the current project. Kinetic analysis of 18F-fluorocholine PET/CT images is being pursued as an alternative method of sextant localization of primary prostate cancer through a collaboration with Phillips Research (Phillips Medical Systems, N.A.). A proposal for a clinical trial studying 18F-fluorocholine PET/CT for whole-body staging in advanced prostate cancer has been reviewed favorably by the National Institutes of Health/ National Cancer Institute. Based on a first-submission percentile score of 12.3%, this project has a high likelihood of funding in 2009.

BACKGROUND

In 2008, there will be an estimated 186,320 new cases and 28,660 deaths from prostate cancer. Prostate cancer remains the second leading cause of male cancer death in the United States. However, a low ratio of deaths to incidence underscores the fact that treatment for early and localized prostate cancer is potentially curable. If treated at an organ-confined stage, the expected 5-year survival from prostate cancer is 100% as compared to a 33% 5-year survival for metastatic prostate cancer. *(1)*. In vivo imaging capable of localizing prostate cancer may increase the rate of early detection and improve pre-treatment risk stratification and treatment decision-making.

BODY

Items Relevant to SOW Task 1: Study Preparation

This is a completed task. The final protocol revision, which added PET/CT as part of the study, was approved on 12 July 2007 by The Queen's Medical Center (QMC) Research & Institutional Review Committee (RIRC, ie. IRB) and on 24 September 2007 by the Tripler Army Medical Center (TAMC) Human Use Committee. There have been no further methodological changes to the study protocol. Following completion of study accrual in June 2008, the study was closed to further enrollment. Completion notification was acknowledged by the QMC RIRC on 9 June 2008. Approval for study continuation limited to data analysis without enrollment was obtained from TAMC on 20 November 2008 with an

expiration date of 26 October 2009. A Closure Acceptance Memorandum from the USAMRMC Human Research Protection Office was received on 20 August 2008.

Items Relevant to SOW Tasks 2: Subject Recruitment and Data Collection

Ten additional human subjects were recruited during the period covered in this report, resulting in 25 total subjects recruited for the study. Of these 10 subjects, 6 were recruited from TAMC. Five of these subjects underwent 18F-fluorocholine PET/CT imaging at TAMC. One subject underwent 18F-fluorocholine PET/CT imaging at QMC before the PET/CT at TAMC became operational. Data from one subject at TAMC was permanently lost due to a computer problem, resulting in 5 complete data sets from Tripler subjects. Four subjects were also recruited from QMC during the no-cost extension period. All QMC subjects underwent PET/CT imaging at QMC, however prostate specimens from 2 of these subjects were not submitted to AFIP for step-section analysis. One specimen, obtained through laparascopic robot-assisted surgery, did not remain intact for step-section histopathology. Another specimen underwent local histopathologic analysis at the request of the attending surgeon immediately after surgery. To replace these missing data sets, 2 additional PET/CT correlated specimens obtained from another study at QMC were analyzed by AFIP and added to the project data. Therefore, a total of 24 complete data sets are available for final study analysis.

Part of task 2d, immunohistochemical staining of specimens for the Ki-67 antigen (ie. MIB-1 staining), has not yet completed. This procedure is being supervised by Dr. Sesterhenn at the AFIP genitourinary department with results expected in February 2009. We expect an invoice in the amount of $25,000 (based on the original proposed budget) from AFIP covering work performed for the project from 2005 to 2009.

Items Relevant to SOW Task 3: Data Analyses

PET/CT image analysis and basic step-section histopathology was completed during the no-cost extension period. Average prostate specimen weight was 46 grams (s.d. 23 grams). Average total tumor volume per specimen was 8.2 cc (s.d. 9 cc). Gleason sum score (GS) distribution is as follows: 13 patients with GS6, 8 with GS7, 1 with GS8, and 2 with GS9. Accuracy of sextant detection of prostate cancer based on measured 18F-fluorocholine uptake in the prostate gland was assessed by receiver operating characteristic (ROC) analysis using methods identical to that of the previous interim analysis (which are described in detail in reprint #1 of appendix 2). However, 2 patients who received anti-androgen therapy prior to surgery were excluded from the ROC analysis since the PET/CT images from both these patients showed globally diminished prostatic activity while step-section histopathology revealed significant "treatment-effects" which could potentially bias the ROC analysis. Based on data from the remaining 22 patients, the estimated area under the ROC curve (AUC) was 0.80 (sensitivity 82% if specificity 60%), which is not significantly different than the previous estimated AUC of 0.82 (sensitivity 85% if specificity 62%) based on 15 initial subjects (from reprint #1, appendix 2).

Final analysis and manuscript preparation will be completed after histopathologic analysis of tumor Ki-67 proliferation index is completed by AFIP. Specimens from the 2 patients who received anti-androgens before surgery will be included in the Ki-67 proliferation analysis, since the modulating effect of anti-androgens on PET uptake correlated to a proliferation index is worth studying. A remaining labor budget of $12,000 is available to cover PI salary and expenses in 2009, in addition to a remaining budget of $1200 for travel. This can be covered through a no-cost extension since not all of the

remaining salary funding was used in 2008 as a result of the PI having to reduce his research hours in 2008 to address an increase in clinical workload caused by the unexpected death of a physician in the PI's clinical practice. As of January 1, 2009, this clinical manpower shortage was corrected, resulting in time available for the PI to complete the project in 2009.

Items Relevant SOW Task 4: Reporting and Design of Secondary Studies

The current project has led to the development of two subsequent projects. The new PET/CT devices incorporated into the project in 2007 brought a significant increase in computing power and storage capacity over the previous PET scanner at QMC. The PET/CT installed at QMC incorporates parallel processing, time-of-flight image reconstruction, and list-mode data acquisition, in addition to improvements in crystal count-rate performance and temporal resolution. These improvements have enabled routine dynamic PET measurement of tissue uptake ("velocities") in addition to standard PET measurements of static tracer uptake ("concentration") as was originally proposed. Preliminarily, the kinetic parameters measured by dynamic PET/CT are comparable in overall accuracy to the static uptake measures from conventional PET, although kinetic measurement does have practical advantages with regards to shorter imaging times and less susceptibility to certain physiologic artifacts (see reprint #5 in appendix 2). Based on these results, the PI began a research collaboration with Philips Research North America (Briarcliff Manor, NY) to further develop kinetic analysis tools for prostate and tumor imaging using 18F-fluorocholine PET/CT. As a medical device company, Philips has the specific expertise and commercial interest relevant to developing image analysis tools for clinically-relevant applications of 18F-fluorocholine PET/CT.

Additionally, much shorter image acquisition times are feasible with the new PET/CT devices, making it practical to expand the research scope to whole-body staging with 18F-fluorocholine PET/CT. With PET/CT, a "whole-body" scan can be completed in less than 30 minutes, compared to 1 hour as was required with the previous generation of stand-alone PET. Using a combined whole-body (static) and prostate (dynamic) imaging technique, we have begun to investigate the effects of various treatments (radiation, hormone, chemotherapy) on prostatic and metastatic tumor uptake of 18F-fluorocholine (see reprint #3 and #4 in appendix 2). Pre-treatment data on prostatic 18F-fluorocholine uptake obtained by the current project will serve as baseline data for studying the effects of various treatments on prostatic 18F-fluorocholine uptake in subsequent studies. The PI has submitted a grant proposal to the National Cancer Institute to investigate 18F-fluorocholine PET/CT for monitoring therapeutic response to chemotherapy and hormone therapy in advanced metastatic prostate cancer (1R21CA139687). The proposal received a favorable priority score of 145 corresponding to a percentile rank of 12.3% and has been resubmitted for FY2009 funding consideration pending an expected increase in NIH budget in 2009.

Labor	12,000
Purchased Services (AFIP)	25,000
Travel	1,200
Admin Supplies	700
Indirect Costs (67%)	26,063
TOTAL	**$ 64,983**

Table: Remaining budget for the 2009 no-cost extension period

KEY RESEARCH ACCOMPLISHMENTS

- The overall accuracy for sextant-based diagnosis of prostate cancer using 18F-fluorocholine PET/CT has been estimated using a gold-standard method of histopathologic reference.

- Two new research projects are based on the results of the current project: 1) A study of kinetic parametric prostate imaging with 18F-fluorocholine PET/CT, conducted in collaboration with Phillips Research NA, and 2) a grant proposal for whole-body post-treatment monitoring and staging using 18F-fluorocholine PET/CT in androgen-insensitive and hormone-refractory prostate cancer submitted to the National Cancer Institute.

REPORTABLE OUTCOMES

The following reports are in addition to those listed in the 2006 and 2007 reports:

2008 PUBLICATIONS:

Kwee SA, Thibault G, Stack R, Coel M, Furusato B, Sesterhenn I. Use of Step-Section Histopathology to Evaluate 18F-Fluorocholine PET Sextant Localization of Prostate Cancer. Molecular Imaging 2008. Jan-Feb;7(1): 12-20.

Kwee SA, Degrado T. Prostate biopsy guided by 18F-fluorocholine PET in men with persistently elevated PSA levels. Eur J Nucl Med Mol Imaging. 2008 Aug; 35(8): 1567-9.

2009 MEETING ABSTRACTS, PRESENTATIONS, AND CONFERENCE PAPERS:

Kwee SA, Coel MN, Lim J. Longitudinal 18F-fluorocholine PET/CT imaging in prostate cancer patients with increased risk of disease progression. 56th Annual Meeting of the Society of Nuclear Medicine. Toronto, Canada. June 13-17, 2009.

Kwee SA, Ly B, Coel MN. RECIST measurability of 18F-fluorocholine PET/CT detected lesions in androgen insensitive prostate cancer. 56th Annual Meeting of the Society of Nuclear Medicine. Toronto, Canada. June 13-17, 2009.

Narayanan M, Kwee SA, Coel MN, Lim J. Kinetic analysis of 18F-fluorocholine PET/CT images for sextant localization of primary prostate cancer. 56th Annual Meeting of the Society of Nuclear Medicine. Toronto, Canada. June 13-17, 2009.

CONCLUSION

Human subjects accrual for this project was completed in 2008. A final one-year no-cost extension for a period of 20 December 2008 to 19 December 2009 is requested in order to complete final immunohistochemical analysis (proliferation index assays) of prostate specimens at the Armed Forces Institute of Pathology. Two subsequent research projects were initiated based on the results of the current project. One project is a research collaboration to develop clinically relevant image analysis tools for measuring the kinetics of 18F-fluorocholine activity in the prostate gland using PET/CT. The second project is a clinical trial proposal to assess treatment responses using 18F-fluorocholine PET/CT in advanced prostate cancer.

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3.   Kwee SA, Wei H, Sesterhenn I, Yun D, Coel MN. Localization of primary prostate cancer with dual-phase 18F-fluorocholine PET. *J Nucl Med.* 2006;47(2):262-269.
4.   Kwee SA, Coel MN, Lim J, Ko JP. Combined use of F-18 fluorocholine positron emission tomography and magnetic resonance spectroscopy for brain tumor evaluation. *J Neuroimaging.* 2004;14(3):285-289.
5.   Kwee SA, Coel MN, Lim J, Ko JP. Prostate cancer localization with 18fluorine fluorocholine positron emission tomography. *J Urol.* 2005;173(1):252-255.
6.   Surti S, Karp JS, Popescu LM, Daube-Witherspoon ME, Werner M. Investigation of time-of-flight benefit for fully 3-D PET. *IEEE Trans Med Imaging.* 2006;25(5):529-538.

APPENDIX 1: Statement of Work (Revised July 2006)

Cancer Localization in the Prostate with F-18 Fluorocholine Positron Emission Tomography

Task 1. Study Preparation, Months 1-4:

 a. Finalize research protocol and study-specific forms.

 b. Obtain institutional review board (IRB) approval of study protocol and consent form at project sites: Tripler Army Medical Center (TAMC), Queen's Medical Center (QMC), and the Armed Forces Institute of Pathology (AFIP).

 c. Orient all study personnel on protocol and methods.

Task 2. Subject Recruitment and Data Collection, Months 4-20:

 a. Begin subject recruitment at TAMC and QMC. A total of 25 subjects will be recruited from both sites over a 16 month period.

 b. Subjects will undergo whole-body F-18 FCH PET or PET/CT scanning to acquire images of the prostate gland.

 c. Subjects not undergoing PET/CT will undergo a separate CT at QMC.

 d. Following surgery, the prostatectomy specimens will delivered to AFIP for processing and analysis. Analysis procedures include surgical histopathology and immunohistochemical staining for the Ki-67 antigen. The data will be recorded on study-specific pathology forms.

 e. All data will be entered into a study database for analysis.

Task 3. Data Analyses, Months 6 – 20:

 a. PET or PET/CT image analysis will be performed by two physicians.

 b. Collected data will be analyzed and correlated in periodic interim analyses. Interim results will be summarized in annual reports.

Task 4. Final Analyses/Reporting and Design of Secondary Studies, Months 20-24:

 a.   Finalize analysis of data and summarize results as stated in the specific aims.

 b. Prepare final report and manuscripts for publication.

 c. Design secondary studies using the collected data.

APPENDIX 2:

REPRINTS ATTACHED ON SUBSEQUENT PAGES:

1. Kwee SA, Thibault G, Stack R, Coel M, Furusato B, Sesterhenn I. Use of Step-Section Histopathology to Evaluate 18F-Fluorocholine PET Sextant Localization of Prostate Cancer. Molecular Imaging 2008. Jan-Feb;7(1): 12-20.

2. Kwee SA, Degrado T. Prostate biopsy guided by 18F-fluorocholine PET in men with persistently elevated PSA levels. Eur J Nucl Med Mol Imaging. 2008 Aug; 35(8): 1567-9.

2009 MEETING ABSTRACTS, PRESENTATIONS, AND CONFERENCE PAPERS:

3. Kwee sA, Coel MN, Lim J. Longitudinal 18F-fluorocholine PET/CT imaging in prostate cancer patients with increased risk of disease progression. 56th Annual Meeting of the Society of Nuclear Medicine. Toronto, Canada. June 13-17, 2009.

4. Kwee SA, Ly B, Coel MN. RECIST measurability of 18F-fluorocholine PET/CT detected lesions in androgen insensitive prostate cancer. 56th Annual Meeting of the Society of Nuclear Medicine. Toronto, Canada. June 13-17, 2009.

5. Narayanan M, Kwee SA, Coel MN, Lim J. Kinetic analysis of 18F-fluorocholine PET/CT images for sextant localization of primary prostate cancer. 56th Annual Meeting of the Society of Nuclear Medicine. Toronto, Canada. June 13-17, 2009.

Use of Step-Section Histopathology to Evaluate ^{18}F-Fluorocholine PET Sextant Localization of Prostate Cancer

Sandi A. Kwee, Gregory P. Thibault, Richard S. Stack, Marc N. Coel, Bungo Furusato, and Isabell A. Sesterhenn

Abstract

To assess positron emission tomography (PET) with fluorine-18 fluorocholine for sextant localization of malignant prostate tumors. Histopathologic analysis was performed on step-sectioned whole-mounted prostate specimens from 15 patients who underwent PET with fluorocholine prior to radical prostatectomy. The maximum standardized uptake value (SUVmax) corresponding to prostate sextants on PET was measured by region of interest analysis and compared with histopathologic results. Histopathology demonstrated malignant involvement in 61 of 90 prostate sextants. The mean total tumor volume per specimen was 4.9 mL (range 0.01–28.7 mL). Mean SUVmax was 6.0 ± 2.0 in malignant sextants and 3.8 ± 1.4 in benign sextants ($p <$ .0001). The area under the receiver operating characteristic curve was 0.82 for sextant detection of malignancy based on SUVmax measurement. Tumor diameter directly correlated with sextant SUVmax in malignant sextants ($r =$ .54, $p <$ .05). In 13 subjects, the largest tumor in the specimen corresponded to the sextant with the highest SUVmax. Fluorocholine PET can serve to localize dominant areas of malignancy in patients with prostate cancer. However, PET with fluorocholine may fail to identify sextants with smaller volumes of malignancy.

PROSTATE CANCER is the second leading cause of cancer death in American men over 50 years of age. The diagnosis of prostate cancer is typically obtained after transrectal ultrasound-guided prostate biopsy. However, this method of diagnosis is prone to sampling error; consequently, a large number of clinically significant prostate cancers are missed at the initial biopsy.[1–5] Although advancements have been made at alternatively detecting primary prostate cancer with ultrasonography or magnetic resonance imaging (MRI), not all of the clinical and technical hurdles associated with these techniques have been overcome.[6–8]

Positron emission tomography (PET) offers an alternative approach for detecting tumors through noninvasive measurement of metabolic changes at the cellular level. This technique works by depicting the biochemical interactions of radiolabeled tracers in vivo. Fluorine-18 (^{18}F)-labeled fluorocholine is a synthetic derivative of choline that is being investigated as a potential tumor imaging agent for PET. The phosphorylation of fluorocholine by choline kinase, an enzyme commonly overexpressed in malignancy, is responsible for the intracellular trapping of this compound.[9] The observation that there is increased choline metabolism in malignant prostate tissue relative to normal tissue supports the possibility of using fluorocholine PET to visualize cancer in the prostate gland.[10,11]

The objective of this histopathologic correlation study was to preliminarily evaluate PET with ^{18}F-fluorocholine for sextant-level localization of malignancy in the prostate gland. The definition of prostate sextants is based on the prostate biopsy convention in which the prostate gland is divided into basal, mid-, and apical portions on each side.[4,7,12–14] PET scanning with fluorocholine was performed prospectively in subjects with organ-confined prostate cancer who subsequently underwent radical prostatectomy. Step-sectioning of completely embedded

Molecular Imaging, Vol 0, No 0 (month 2008): pp 000–000   **1**

Molecular Imaging   MI_2008_00002.3d   10/1/08   14:30:52
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prostate specimens was used to obtain the diagnostic standard of reference for this study.

Materials and Methods

Human subjects research approval for this study was obtained from the participating hospitals' institutional review board and the Department of the Defense Human Subjects Research and Review Board. To meet inclusion criteria for the study, subjects had to have clinically organ-confined prostate cancer (stage II) for which radical prostatectomy was elected as primary treatment. Written informed consent was obtained from all subjects prior to their involvement with the study.

Radioactive Tracer Synthesis

Synthesis of ^{18}F- fluorocholine was performed by fluorination of ditosylmethane with fluorine-18 followed by alkylation of fluorotosylmethane with dimethylethanolamine. The synthesis procedure was automated and performed at an on-site cyclotron laboratory using a computer-controlled chemical process control unit (CTI/Siemens CPCU, CTI/Siemens, Knoxville, TN).[15] All synthesis products passed standard assays for radiochemical purity, radionuclidic identity, chemical purity, sterility, and pyrogenicity in compliance with US Pharmacopia Good Clinical Practice guidelines.

Imaging

PET was performed in the supine position after a 3-hour fast. All PET scans were obtained with a 32-ring whole-body PET scanning instrument (SHR-22000, Hamamatsu Photonics KK, Hamamatsu City, Japan). Whole-body transmission scans were first acquired using two germanium 68 rod sources over five fields of view (FOV) for 3 minutes each. After transmission scanning, 3.3 to 4 Mbq/kg of ^{18}F-fluorocholine was administered through an antecubital vein. After a 10-minute delay, two-dimensional emission scans were acquired for 7 minutes over each FOV. Imaging proceeded in a cephalad direction starting at the pelvis. The PET images were reconstructed using an ordered subsets expectation maximization algorithm. Segmented attenuation correction was applied to the emission data using the measured transmission data. Reconstruction resulted in 4 mm × 4 mm × 3.6 mm voxels. Images were viewed and analyzed on a workstation using PET image analysis software (Medasys Data Systems, Gif-sur-Yvette Cedex, France).

Immediately following PET, computed tomography (CT) of the pelvis (slice thickness 3.2 mm, reconstruction interval 2.0 mm) was performed without intravenous contrast using a conventional CT scanner (multislice four-slice CT, Philips Medical Systems, Shelton, CT). The CT images were spatially registered to the PET images using commercial software (HERMES, Hermes Medical Solutions, Battle Ground, WA). Images were reviewed and analyzed on computer workstations.

Image Analysis

Image analysis was performed by two independent readers with PET imaging experience (S.A.K., M.N.C.). The readers were blinded to the histopathology results at the time of the initial reading, although it was known that all subjects were diagnosed with prostate cancer. Analysis began with visual inspection of CT-registered PET images to identify the prostate. The prostate can be identified on fluorocholine PET images as a discrete region of uptake located inferior and slightly posterior to the urinary bladder (Figure 1). Measurement of uptake in prostate sextants was performed as follows: prostate volumes on CT-registered PET images were manually segmented into sextants consisting of an upper (basal) one-third, middle one-third, and lower (apical) one-third portion of the gland on each side. Using region of interest analysis, the maximum standardized uptake value (SUVmax) corresponding to prostate sextants on each image slice was measured and the SUVmax of each sextant was recorded. SUVmax was defined as the maximum measured activity divided by the injected radioactivity normalized to body weight. The individual readers obtained concordant sextant SUVmax measurements in all subjects.

Prostate Specimen Analysis

After surgery, the prostate specimens were placed in a 10% formalin solution for 3 days. Histologic processing of the prostate specimen was then performed by the step-section technique. Completely embedded whole-prostate specimens were sectioned at regular 2.2 mm intervals. Thin slices from each section were mounted on large glass slides and stained with hemotoxylin and eosin. Areas of malignant tumor on each slide were manually segmented and assigned to their corresponding sextant by a single pathologist with extensive experience in genitourinary pathology (I.A.S.). Each slide was photographed to scale using a digital camera mounted on a stage (Figure 2). The
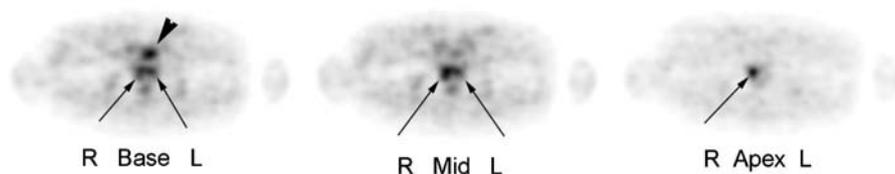
Figure 1. Transverse axial fluorocholine positron emission tomographic images of the prostate. In this example, a malignant tumor demonstrates increased fluorocholine uptake from the base to the apex of the prostate (*long arrows* point to malignant prostate sextants). Urinary excretion of fluorocholine is evident in the urinary bladder (*large arrowhead*) but did not interfere with prostate visualization.
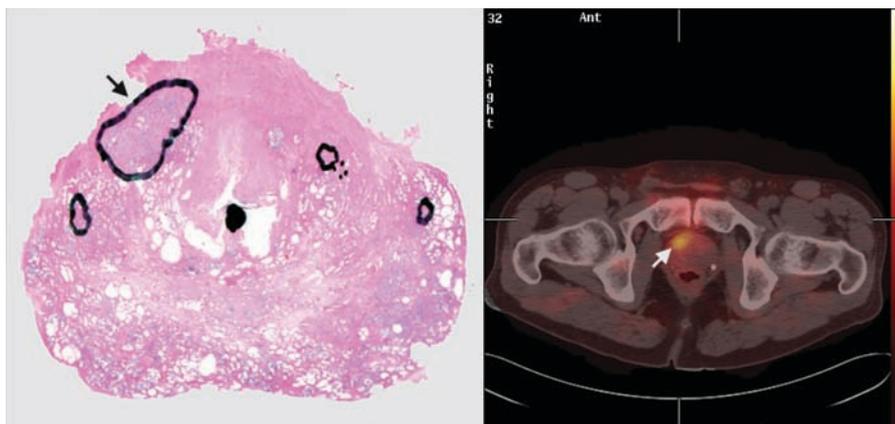
Figure 2. *Left*, Micrograph (×10) of a prostate specimen containing multiple malignant tumors (*outlined in black*). The largest malignant tumor is located in the anterior right base (*black arrow*). It measures 1 cm in largest diameter. *Right*, The corresponding transverse axial computed tomography–fused positron emission tomographic (PET) image of the pelvis demonstrates highest fluorocholine uptake (*white arrow*) in the area to the largest malignant tumor found by histopathology. Smaller malignant tumors in the specimen were not distinctly evident on fluorocholine PET.

size, Gleason scoring, and sextant location of all malignant tumors were recorded for each specimen.

Analysis and Statistical Considerations

Statistical analysis was performed at the prostate sextant level, with histopathologic findings serving to determine the presence or absence of malignancy in each sextant. Sextants were classified as malignant if they contained a portion of at least one malignant tumor regardless of its size. Statistics included sensitivity and specificity for sextant diagnosis using various SUVmax thresholds for defining malignancy in prostate sextants based on receiver operating characteristic (ROC) analysis. Differences in sample means were tested for significance using the Student *t*-test. The linear relationship between two variables was assessed using the Pearson correlation coefficient. Statistical analysis was performed using *JMP* version 5 (SAS Institute Inc., Cary, NC). All tests were two-sided, and *p* values < .05 were considered significant.

Results

Subject Characteristics

Fifteen subjects underwent preoperative fluorocholine PET with whole-prostate histopathologic analysis of their specimens after surgery. Individual subject characteristics are summarized in Table 1. The average age of the subjects was 62 years (range 47–71 years). The median serum prostate-specific antigen (PSA) level was 5.1 ng/mL (range 3.5–13.8 ng/mL). The mean weight of prostate specimens was 50 g (range 13–106 g). Multifocal prostate cancer was found in 13 subjects and unifocal prostate cancer in 2 subjects. Benign prostatic hyperplasia or prostatitis was evident in every prostate examined. Sixty-one of 90 prostate sextants were found to harbor malignant tumors on histopathologic analysis. The median number of malignantly involved sextants was 4 (range 2–6). The mean total tumor volume per specimen was 4.9 mL (range 0.01–28.8 mL). The median Gleason sum score was 6 (range 6–9).

PET Images

The SUVmax of the prostate and the SUVmax of the sextant containing the largest tumor for each subject is listed in Table 1. The mean SUVmax of malignant sextants was significantly higher than the mean SUVmax of benign sextants (6.0 ± 2.0 vs 3.8 ± 1.4, respectively; *p* < .0001). The area under the ROC curve was 0.82 for fluorocholine PET detection of malignant prostate sextants (Figure 3). The highest diagnostic accuracy was achieved using a

Table 1. Characteristics of 15 Subjects Who Underwent Fluorocholine Positron Emission Tomography Prior to Radical Prostatectomy with Whole-Mount Histopathologic Analysis of Their Prostate Specimens

Subject	Age (yr)	PSA (ng/mL)	Gleason Sum	Prostate Weight (g)	Total Malignant Tumor Volume (mL)	No. of Malignant Sextants	Diameter of Largest Malignant Tumor (mm)	Sextant SUVmax of Largest Malignant Tumor	SUVmax of Prostate
1	58	3.5	3 + 3	27.7	5.7	5	23	6.9	6.9
2	47	4	3 + 3	46.3	4.2	6	26	11.3	11.3
3	54	5	3 + 3	12.9	5.0	3	18	4.9	4.9
4	52	4	4 + 3	25.8	1.7	4	13	3.5	3.5
5	63	6.5	3 + 3	104.6	0.03	2	4	4.1	4.1
6	63	5.1	3 + 4	49.9	0.5	2	9	5.8	5.8
7	57	8.1	3 + 3	34.2	0.05	3	3	3.2	3.2
8	62	4.2	3 + 3	33.5	9.3	6	25	4.5	4.5
9	63	7.1	3 + 3	49.3	1.7	5	20	6.9	6.9
10	62	5	4 + 5	41.9	14.0	5	33	7.0	7.0
11	71	6.3	3 + 3	43.6	5.9	6	18	7.3	7.3
12	68	10.2	3 + 4	36.7	28.7	4	33	7.2	7.2
13	66	3.5	3 + 3	62.8	1.1	4	16	7.0	7.3
14	67	10	3 + 3	82.1	0.2	4	5	3.6	4.1
15	66	13.8	3 + 3	106.1	0.2	4	2	7.1	7.1

PSA = prostate-specific antigen; SUVmax = maximum standardized uptake value.

sextant SUVmax of 5.6 or higher to classify a sextant as malignant. At this point of the ROC curve, accuracy, sensitivity, and specificity were 72%, 64%, and 90%, respectively. With lower SUVmax threshholds, sensitivity can be increased at the cost of specificity. For example,
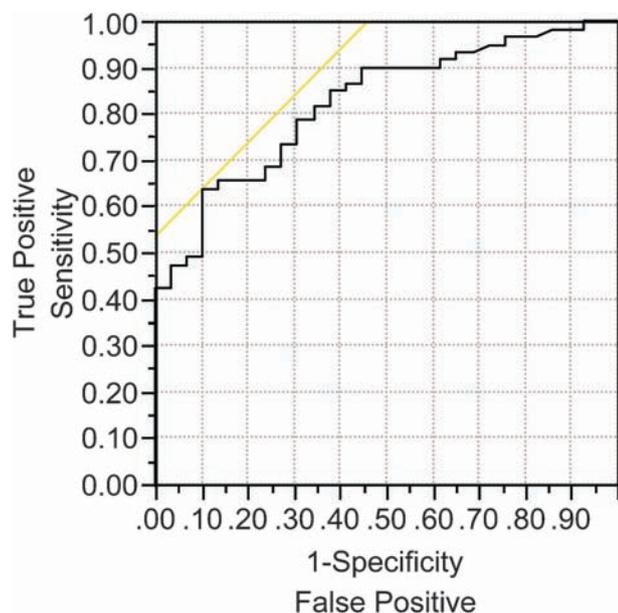
Figure 3. Receiver operating characteristic curve for fluorocholine positron emission tomogrpahic diagnosis of malignant prostate sextants (regardless of tumor size). Area under the curve = 0.82.

sensitivity and specificity were 85% and 62%, respectively, using a SUVmax threshold of 4.0.

In all subjects, the highest SUVmax of the prostate was localized to a malignant sextant. In 13 of 15 subjects, the sextant with the highest SUVmax was also the sextant containing the largest tumor of that specimen. There was a statistically significant correlation between maximum tumor diameter and SUVmax in malignant sextants (Pearson correlation coefficient $r = .54$, $p < .05$) (Figure 4). There were no significant correlations between highest SUVmax in the prostate, subject's age, serum PSA, and Gleason sum score.

Discussion

The prostate gland is a challenging organ to image with nuclear techniques because of its anatomic location and small size relative to the spatial resolution of most nuclear imaging devices. The spatial resolution of PET is influenced not only by detector design and reconstruction method but also by the physical effects of radioactive scatter and positron travel.[16] Because of these factors, there is spillover of radioactive signals from small sources, which leads to larger but dimmer sources on the final reconstructed PET image. The finding of a correlation between the SUVmax of malignant sextants and tumor size
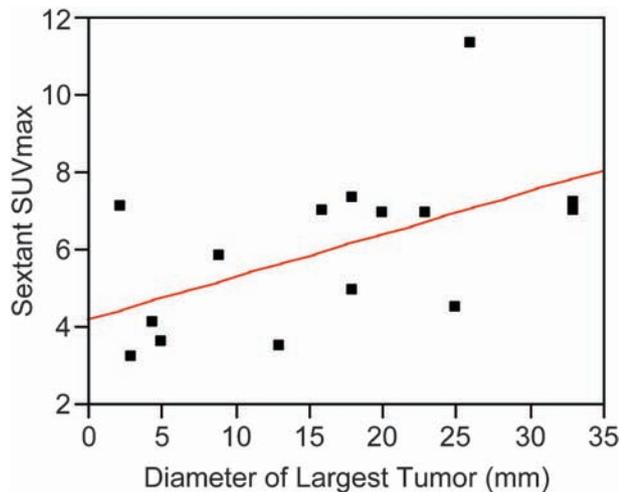
Figure 4. Sextant maximum standardized uptake value (SUVmax) as a function of largest tumor diameter in malignant sextants.

in this study is attributable in part to the limited spatial resolution of current PET instrumentation.

For very small tumors, there is also a partial volume effect owing to the fact that SUV is a reflection of the average radioactivity concentration in a volume of tissue that corresponds to an image voxel.[17] Assuming that fluorocholine is concentrated by malignant cells, the measured SUV of a voxel-sized volume containing both malignant and benign cells should be lower than the measured SUV of the same volume of tissue containing only malignant cells. Despite this limitation in quantitative assessment with SUVmax, the measurement of sextant SUVmax on fluorocholine PET provided a degree of accuracy that was comparable to that of endorectal MRI, magnetic resonance spectroscopy, and carbon 11 choline PET for sextant-level detection of prostate cancer.[7,18–20] Given that prognosis in prostate cancer may be related to tumor size,[21,22] a lower sensitivity for small malignant lesions may be acceptable in the appropriate clinical context.

The relatively small tumor volumes found in those enrolled in this study were not surprising since the majority of subjects were from a young military population that has undergone periodic screening for prostate cancer. The fact that fluorocholine PET has performed reasonably well in this group of lower-risk patients was encouraging. In this study, the sextant with the highest SUVmax was consistently malignant and often corresponded to the site of highest tumor volume in the specimen. These findings support the possibility of using fluorocholine PET as an imaging adjunct for directing prostate biopsies (to the areas of highest malignant

potential) or for assisting with prostate radiation therapy planning (with the goal of delivering higher radiation doses to the densest areas of malignancy).

The use of SUVmax in this study provided a reproducible, objective measure for classifying the prostate sextant. However, when objective threshold values are applied to produce a dichotomous result, there is usually a trade-off between diagnostic sensitivity and specificity that is a function of the threshold value.[23] Although an SUVmax threshold of 5.6 resulted in the highest overall accuracy in this study, certain clinical applications, such as prostate biopsy, may benefit from a higher sensitivity achieved through using a lower SUVmax threshold. Appropriate SUVmax thresholds should be selected based on clinical requirements.

A previous study evaluating prostate PET/CT with fluorocholine reported no significant difference in fluorocholine uptake between malignant and benign prostate lesions.[24] However, there were differences in imaging technique between this and the current study. In particular, prostate imaging in this previous study was begun at 2 minutes postinjection of fluorocholine, whereas in the present study, imaging was begun at 10 minutes postinjection. Although tissue uptake of fluorocholine is indeed rapid, a 2-minute delay before imaging may not have been sufficient to allow visualization of malignant prostate tumors.[9,25] In a previous study, we also observed the ratio of fluorocholine uptake between malignant and benign areas of the prostate to increase significantly over the interval of 10 minutes to 1 hour postinjection.[26] Further study is needed to determine the optimal fluorocholine PET scan protocol for evaluating prostate tumors.

With delayed imaging, there is an increase in the amount of bladder radioactivity encountered. This is the result of urinary excretion of fluorocholine or its metabolites. Although the effects of urinary bladder activity on prostate image interpretation have not been studied specifically, it is conceivable that radioactive scatter from the bladder can lead to both false-positive and false-negative results. If bladder radioactivity can be reduced, it may be possible to improve the overall diagnostic accuracy of fluorocholine PET for prostate tumor diagnosis. Dynamic imaging and protocols to minimize urinary bladder radioactivity may be useful in future PET–computed tomographic (CT) studies to further optimize fluorocholine PET for prostate imaging.

The results of this study should be considered in light of several limitations. First, the accuracy of fluorocholine PET was assessed only in patients with known prostate

Table 2. Sextant Malignancy and Maximum Standardized Uptake Value

Subject	Sextant	Malignant (1 = yes, 0 = no)	Tumor > 0.5 cm (1 = yes, 0 = no)	Sextant SUVmax
1	RB	1	1	6.9
	LB	1	1	6.6
	RM	1	1	6.5
	LM	1	1	5.8
	RA	1	1	4.9
	LA	0	0	4.9
2	RB	1	1	10.3
	LB	1	1	11.3
	RM	1	1	9.8
	LM	1	1	10.0
	RA	1	1	10.4
	LA	1	1	7.8
3	RB	0	0	3.2
	LB	1	1	4.6
	RM	0	0	3.1
	LM	1	1	4.9
	RA	0	0	2.2
	LA	1	1	3.8
4	RB	0	0	2.6
	LB	1	1	3.5
	RM	0	0	1.7
	LM	1	1	2.7
	RA	1	0	2.2
	LA	1	0	2.5
5	RB	0	0	3.4
	LB	0	0	3.3
	RM	0	0	3.5
	LM	0	0	3.7
	RA	1	0	4.1
	LA	1	0	3.6
6	RB	1	1	5.4
	LB	0	0	3.3
	RM	1	1	5.8
	LM	0	0	3.5
	RA	0	0	2.9
	LA	0	0	2.6
7	RB	0	0	2.3
	LB	1	0	3.2
	RM	0	0	2.5
	LM	0	0	2.2
	RA	1	0	3.2
	LA	1	0	3.0
8	RB	1	1	4.0
	LB	0	0	3.0
	RM	1	1	4.5
	LM	0	0	3.9
	RA	1	1	4.4
	LA	0	0	4.1

Table 2. Continued

Subject	Sextant	Malignant (1 = yes, 0 = no)	Tumor > 0.5 cm (1 = yes, 0 = no)	Sextant SUVmax
9	RB	1	1	4.4
	LB	1	1	6.5
	RM	1	1	5.6
	LM	1	1	6.9
	RA	1	1	4.0
	LA	1	1	4.7
10	RB	1	1	5.8
	LB	0	0	5.3
	RM	1	1	7.0
	LM	1	1	6.8
	RA	1	1	5.7
	LA	1	1	5.9
11	RB	1	1	4.1
	LB	1	1	4.4
	RM	1	1	6.5
	LM	1	1	7.2
	RA	1	1	7.3
	LA	1	1	6.5
12	RB	1	1	6.9
	LB	1	1	7.0
	RM	0	0	4.5
	LM	1	1	7.2
	RA	0	0	4.2
	LA	1	1	5.7
13	RB	0	0	6.5
	LB	0	0	6.5
	RM	1	1	7.0
	LM	1	1	7.3
	RA	1	1	6.1
	LA	1	1	7.0
	RB	0	0	5.4
14	LB	1	0	6.6
	RM	1	0	6.4
	LM	1	0	6.7
	RA	0	0	6.4
	LA	1	0	6.6
15	RB	0	0	5.5
	LB	0	0	4.9
	RM	1	1	7.8
	LM	1	1	6.2
	RA	1	1	6.7
	LA	1	1	7.1

LA = left apex; LB = left base; LM = left mid; RA = right apex; RB = right base; RM = right mid; SUVmax = maximum standardized uptake value.

cancer. Therefore, the results of this study cannot be applied to patients who are only suspected of having cancer. For example, the utility of fluorocholine PET in patients with elevated PSA levels and negative initial prostate biopsies requires specific study. Furthermore, the sextant assignment of malignant tumors on histopathology and the measurement of sextant SUVmax were performed by different individuals. Although this ensures independence between the diagnostic test and gold standard interpretations, there is the possibility that sextants defined

Table 3. Receiver Operating Characteristic Curve for Sextant Maximum Standardized Uptake Value as a Discriminator for Sextants Containing Malignant Tumors

SUVmax	1-Specificity	Sensitivity	True Positive	True Negative	False Positive	False Negative
11.34	0	0.0164	1	29	0	60
10.41	0	0.0328	2	29	0	59
10.33	0	0.0492	3	29	0	58
9.96	0	0.0656	4	29	0	57
9.79	0	0.082	5	29	0	56
7.81	0	0.0984	6	29	0	55
7.75	0	0.1148	7	29	0	54
7.33	0	0.1311	8	29	0	53
7.3	0	0.1475	9	29	0	52
7.17	0	0.1639	10	29	0	51
7.15	0	0.1803	11	29	0	50
7.09	0	0.1967	12	29	0	49
7.04	0	0.2131	13	29	0	48
7.01	0	0.2295	14	29	0	47
6.98	0	0.2623	16	29	0	45
6.91	0	0.2787	17	29	0	44
6.9	0	0.2951	18	29	0	43
6.87	0	0.3115	19	29	0	42
6.78	0	0.3279	20	29	0	41
6.73	0	0.3443	21	29	0	40
6.68	0	0.3607	22	29	0	39
6.63	0	0.377	23	29	0	38
6.58	0	0.3934	24	29	0	37
6.55	0	0.4098	25	29	0	36
6.52	0	0.4262	26	29	0	35
6.51	0.0345	0.4262	26	28	1	35
6.5	0.0345	0.4426	27	28	1	34
6.47	0.0345	0.459	28	28	1	33
6.46	0.0345	0.4754	29	28	1	32
6.45	0.069	0.4754	29	27	2	32
6.44	0.069	0.4918	30	27	2	31
6.38	0.1034	0.4918	30	26	3	31
6.17	0.1034	0.5082	31	26	3	30
6.11	0.1034	0.5246	32	26	3	29
5.94	0.1034	0.541	33	26	3	28
5.82	0.1034	0.5574	34	26	3	27
5.8	0.1034	0.5738	35	26	3	26
5.78	0.1034	0.5902	36	26	3	25
5.74	0.1034	0.6066	37	26	3	24
5.68	0.1034	0.623	38	26	3	23
5.6	0.1034	0.6393	39	26	3	22
5.51	0.1379	0.6393	39	25	4	22
5.4	0.1379	0.6557	40	25	4	21
5.36	0.1724	0.6557	40	24	5	21
5.31	0.2069	0.6557	40	23	6	21
4.94	0.2414	0.6557	40	22	7	21
4.9	0.2414	0.6721	41	22	7	20
4.89	0.2414	0.6885	42	22	7	19

Table 3. Continued

SUVmax	1-Specificity	Sensitivity	True Positive	True Negative	False Positive	False Negative
4.86	0.2759	0.6885	42	21	8	19
4.7	0.2759	0.7049	43	21	8	18
4.56	0.2759	0.7213	44	21	8	17
4.5	0.2759	0.7377	45	21	8	16
4.49	0.3103	0.7377	45	20	9	16
4.4	0.3103	0.7705	47	20	9	14
4.37	0.3103	0.7869	48	20	9	13
4.19	0.3448	0.7869	48	19	10	13
4.12	0.3448	0.8197	50	19	10	11
4.1	0.3793	0.8197	50	18	11	11
4	0.3793	0.8525	52	18	11	9
3.85	0.4138	0.8525	52	17	12	9
3.81	0.4138	0.8689	53	17	12	8
3.68	0.4483	0.8689	53	16	13	8
3.61	0.4483	0.8852	54	16	13	7
3.51	0.4483	0.9016	55	16	13	6
3.5	0.4828	0.9016	55	15	14	6
3.48	0.5172	0.9016	55	14	15	6
3.37	0.5517	0.9016	55	13	16	6
3.31	0.5862	0.9016	55	12	17	6
3.3	0.6207	0.9016	55	11	18	6
3.2	0.6207	0.9344	57	11	18	4
3.17	0.6552	0.9344	57	10	19	4
3.09	0.6897	0.9344	57	9	20	4
3	0.7241	0.9508	58	8	21	3
2.9	0.7586	0.9508	58	7	22	3
2.74	0.7586	0.9672	59	7	22	2
2.63	0.7931	0.9672	59	6	23	2
2.6	0.8276	0.9672	59	5	24	2
2.5	0.8621	0.9836	60	4	25	1
2.3	0.8966	0.9836	60	3	26	1
2.2	0.931	0.9836	60	2	27	1
2.17	0.931	1	61	2	27	0
2.16	0.9655	1	61	1	28	0
1.68	1	1	61	0	29	0
1.68	1	1	61	0	29	0

on PET may not correspond precisely to sextants defined on the specimen. However, the effects of any potential sextant mismatch are likely small given that sextants correspond to relatively large nonanatomic regions of the prostate. Finally, this study was conducted using a conventional stand-alone PET scanner. Newer technologies such as time-of-flight scanning, list-mode data acquisition, and PET-CT have been introduced that may enable more detailed subsextant, per-sextant, or per-lesion evaluation of the prostate with fluorocholine. By increasing the count-rate performance of PET, time-of-flight may particularly improve the quality of prostate images,

especially in larger patients.[27] PET-CT should enable more accurate anatomic localization of fluorocholine accumulation in the prostate compared with stand-alone PET. These new technologies should be beneficial for future prostate cancer localization studies using fluorocholine.

Conclusion

This histopathologic correlation study in patients with relatively low tumor burdens supports fluorocholine PET as an imaging technique for delineating prostate sextants with malignant involvement. Although there was lower

sensitivity for sextants with small tumor burdens, this technique does appear capable of localizing dominant malignant regions in the prostate and thus may have value for specific clinical applications such as targeted prostate biopsy or prostate radiation therapy dose augmentation.

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Prostate biopsy guided by 18F-fluorocholine PET in men with persistently elevated PSA levels

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We read with interest the paper published in the May 2008 issue of the European Journal of Nuclear Medicine by Igerc et al. titled "The value of ^{18}F-Choline PET/CT in patients with elevated PSA-level and negative prostate needle biopsy for localization of prostate cancer" [1]. In this study, the authors performed fluorocholine positron emission tomography (PET)/computed tomography (CT) of the prostate in 20 patients who have had repeatedly negative prostate biopsies despite persistently elevated prostate specific antigen (PSA) levels. The PET/CT images were interpreted by the authors in a semi-quantitative fashion by measurement of prostatic maximum standardized uptake value (SUVmax) as well as in a subjective fashion, by visually classifying the pattern of prostatic uptake as focal, multifocal, or inhomogeneous. To investigate the source of these patterns of prostatic uptake,

An author's reply to this letter is available at http://dx.doi.org/10.1007/s00259-008-0783-4.

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the authors used the results of subsequent prostate biopsy as the study gold standard. In addition to sextant-based biopsy, the authors directed additional prostate biopsies towards areas corresponding to increased fluorocholine uptake on PET/CT. We congratulate the authors on their work, as it represents the first study of fluorocholine PET/CT in men who have not yet been diagnosed with prostate cancer, but are at increased risk of having the disease in view of having persistently elevated levels of PSA.

This paper contributes to the growing body of evidence suggesting that benign diseases can cause increased fluorocholine uptake in the prostate gland. In our own studies, we also encountered significant overlap in the degree of benign and malignant 18F-labeled choline uptake in the prostate. In a study by Kwee et al., the diagnostic specificity of increased SUVmax for discriminating malignant prostate sextants was found to be as low as 48%, although malignancy was still a frequent finding in areas of the prostate with the highest SUVmax [2]. However, in contrast to the study by Igerc et al., another study by Kwee et al. found 1-h delayed imaging led to an improved malignant-to-benign contrast ratio of uptake in the prostate [3]. Igerc et al. found no improvement in malignant discrimination when imaging the prostate at 30-min post-injection. In attempting to reconcile these disparate findings, we considered several methodological issues warranting further discussion.

First, the authors correctly pointed out that the use of prostate biopsy could introduce bias into their study, since prostate biopsy is prone to sampling error and has known limitations in diagnostic sensitivity. However, the potential impact of such bias may be considerable, since in one study it has been found that biopsy misses over 50% of malignant lesions subsequently found on whole-prostate histologic

examination [4]. Since many patients in the study by Igerc et al. also had enlarged prostate glands, this problem could be magnified, since prostatic enlargement is known to decrease further the diagnostic yield of prostate biopsy [5]. Since the percentage of malignancy in the biopsy core, or number of biopsy specimens, was not reported, we do not know whether the malignant tumors they discovered were relatively small and more likely to have been missed by random biopsy. Regardless, the possibility of bias due to sampling error should be viewed as a considerable limitation of the study.

To help reduce the chance of sampling bias, the authors did direct additional biopsies towards areas in the prostate corresponding to focal fluorocholine accumulation. However, this approach has several pitfalls arising from issues of technical reproducibility. While a description of the biopsy method was not provided by the authors, we assume prostate biopsies were performed in this study via a transrectal approach under ultrasound guidance, as this is the most commonly used prostate biopsy technique. Because the biopsy is performed by hand, there is inherent operator dependence in guiding the biopsy needle. In addition to this possible source of error, the use of a transrectal ultrasound probe would invariably compress and deform the prostate, making it impossible for there to be precise spatial correspondence between a focus of uptake seen on a tomographic PET/CT image and the tip of a biopsy needle as viewed in a non-tomographic 2D ultrasound image of the compressed prostate gland. Therefore, in instances where no malignancy was found to correspond to an area of focal 18F-choline uptake on PET/CT, the possibility of sampling error should be a strong consideration. Since transperineal prostate biopsy under CT stereotactic or robotic guidance is now becoming technically feasible, there are potential opportunities in the future to reduce sampling bias and operator error through "real-time" PET/CT guidance of the prostate biopsy.

With that said, we felt that the study's reported yield of malignant detection in 25% (5/20) of patients undergoing PET/CT directed biopsies showed promise. While 25% is still within range of published re-biopsy detection rates, as well as detection rates of strategic re-biopsy based on statistical approaches or refined biopsy templates, it should be pointed out that the patients studied by Igerc et al. have all undergone at least two previous biopsy procedures with negative results. It therefore remains encouraging that with a single PET directed biopsy, the diagnosis of prostate cancer was finally obtained. While it is beyond the scope of the current study to address the prognostic value of a negative biopsy result following PET-guided biopsy, it would be of additional interest to know whether any of the patients with inhomogenous or multifocal prostatic uptake at the time-of-study biopsy were later diagnosed with

prostate cancer at follow-up. A question for future studies is the likelihood of prostate cancer with a "negative" 18F-choline PET/CT or a negative PET-directed biopsy. Is the likelihood of prostate cancer reduced to the point that patients may defer or delay the next biopsy?

To directly address the question of whether there is better malignant discrimination on delayed 18F-choline PET imaging, it is worth pointing out that DeGrado et al.'s original observation of a plateau in 18F-choline uptake in the prostate by 5-min post-injection was made only in a prostate with known malignant involvement [6]. Therefore, it cannot be assumed that this uptake pattern also applies to benign prostatic lesions or prostate glands with no malignant involvement. Kwee et al. reported decreasing SUVs over 1 h in probable benign areas and either stable or increasing SUVs in malignant areas. Thus, their observed pattern of uptake in malignant prostatic lesions is compatible with DeGrado et al.'s original observation. With regards to washout of 18F-choline from benign tissues, this phenomenon has been recognized in other instances. For example, prominent transient uptake of 18F-choline by histopathologically benign inguinal lymph nodes is frequently encountered and was reported in one of the first papers on prostate cancer imaging with 18F-choline [7]. Retention of 18F-choline in tissues requires metabolic trapping in the form of phosphoryl-[18F]fluorocholine. Certain tumors, such as the experimental 9L-glioma in rats, demonstrate poor metabolic retention of 18F-choline in spite of maintained transport function [8]. Although it remains uncertain whether delayed imaging may have diagnostic value, the pharmacokinetics of 18F-choline in non-malignant tissues does warrant further study.

While study of delayed 18F-choline PET/CT imaging in the study by Igerc et al. was confounded by potential sampling bias related to prostate biopsy, we acknowledge the possibility that any benefit from delayed imaging may be negated if significant urinary bladder or urethral radioactivity is encountered on the delayed prostate images. The authors did not mention whether they found urinary bladder activity to be problematic on their 30-min delayed images, or whether this may have impacted their measurement of prostatic uptake on the delayed scans. With retrospective dynamic scan reconstruction becoming routinely available on new PET/CT scanners, and with improved count-rate performance and temporal resolution in these new devices, it is likely that dual-time-point imaging will be unnecessary. Rather than repeating the scan at two discrete time points, uptake velocities within lesions can be determined over a period of several minutes, and it may even be possible to ascertain perfusion parameters (a potential discriminator for prostate lesions) by analyzing kinetics during the flow phase beginning immediately after injection.

Finally, because all studies to date have been single-institution studies, considerations must also be made with regards to population differences between individual studies. In addition to the obvious difference between studying a group of patients with high PSA who have not yet been diagnosed with cancer versus studying patients already diagnosed with prostate cancer, there are also racial, ethnic, and environmental differences to consider. Significant population differences in the prevalence and biology of benign prostatic hyperplasia and other benign prostatic diseases are known to exist [9, 10]. Several of the early studies of 18F-choline PET/CT imaging of the prostate included a relatively large number of men of Japanese ancestry [2, 3]. With the increasing number of sites performing PET/CT with 18F-choline, it may be feasible to pursue multi-institutional collaborations and multi-center studies with the goals of harmonizing protocols and reducing the potential effects of population bias.

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Print this Abstract

Control Number: 149817

RECIST measurability of 18F-choline PET/CT detected lesions in androgen insensitive prostate cancer. S. A. Kwee[*1], B. Ly[2], M. N. Coel[1]; 1. Hamamatsu/Queen's PET Imaging Center, Honolulu, HI 2. University of Hawaii John A. Burns School of Medicine, Department of Medicine, Honolulu, HI

Objectives: Apply measurability criteria based on the Response Evaluation Criteria in Solid Tumors (RECIST) to lesions found on 18F-choline PET/CT in patients with androgen insensitive prostate cancer (AIPC). **Methods:** Whole-body PET followed by CT or in-line PET/CT using 4 Mbq/kg of 18F-choline was performed on 30 patients with prostate cancer, castrate testosterone levels, and rising post-treatment prostate specific antigen (PSA) levels. PET/CT images were interpreted visually to identify lesions with increased 18F-choline uptake. Lesions were assessed for measurability based on RECIST. **Results:** Lesions showing increased 18F-choline uptake were found in 28/30 (93%) of patients. Thirty-eight of 55 (69%) lesions (from 14 patients) were measurable by RECIST. Three patients were known previously to have RECIST measurable lesions, 17 patients previously had elevated serum PSA level as sole evidence of disease, and 10 patients had metastases noted on prior radionuclide bone scans. Detection of skeletal, prostatic, or RECIST-compatible lesions was more likely with a PSA level greater than 4.0 ng/ml (Fisher exact p = 0.0005). Lymph node maximum standardized uptake value (SUVmax) correlated with node diameter (Pearson r = 0.44, p< 0. 001). **Conclusions:** PET/CT with 18F-choline may allow whole-body detection of RECIST measurable lesions in AIPC, while also detecting skeletal and prostate lesions that may be measurable by other criteria. Therefore, comparisons with conventional response criteria such as RECIST may aid in the evaluation of 18F-choline PET/CT for gauging therapeutic response in AIPC. **Research Support:** This work was supported by U.S. Army Medical Research and Materiel Command grant W81XWH-05-1-0056 (PCRP PC04130).

Other Information:

Presentation Preference: Oral or Poster

Track: Oncology - Clinical Disagnosis

Category: Solid Tumors

Subcategory: Prostate/Genitourinary

FDA Disclosures:

Device/Drug	Fluorine-18 fluoromethylcholine
Status	Investigational

Financial Disclosures:

Sandi Kwee
No Financial Disclosures
Bevan Ly

No Financial Disclosures
Marc Coel
No Financial Disclosures

Print this Abstract

Control Number: 150216

Longitudinal 18F-choline PET/CT imaging in prostate cancer patients with increased risk of disease progression. S. A. Kwee[*1], M. N. Coel[1], J. Lim[1]; 1. The Queen's Medical Center, Hamamatsu/Queen's PET Imaging Center, Honolulu, HI

Objectives: Assess the feasibility of using 18F-choline PET/CT for monitoring disease after treatment in prostate cancer patients at increased risk of treatment failure. **Methods:** Thirteen patients with high-risk (Gleason Score > 7 or prostate specific antigen (PSA) > 20ng/ml) or recurrent prostate cancer underwent up to 4 whole-body 18F-choline PET or PET/CT scans over 5 years. Serial scans were interpreted as showing no evidence of disease (NED), persistent disease, or progressive disease. Differences were assessed by analysis of variance. **Results:** There were 2, 8, 8, 3 and 1 scans performed after prostatectomy, radiation, androgen manipulation, chemotherapy, and no therapy respectively. A significant difference in PSA was detected between patients whose scans showed no increased uptake, increased prostatic uptake only, and increased metastatic uptake (F-value 8.518, p=0.001). Mean PSA levels (in ng/ml) in these groups were 0.59 (sd 0.50), 12.2 (sd 7.1), and 71.5 (sd 65.9) respectively. A significant difference in PSA was also detected between patients whose scans showed NED, persistent disease, and progressive disease after treatment (F-value 5.833, p=0.014). Mean PSA levels in these groups were 0.59 (sd 0.50), 68.4 (sd 61.5), and 96.8 (sd 81.4) respectively. **Conclusions:** PET/CT with 18F-choline may identify potential sites of recurrent or metastatic disease in high-risk prostate cancer patients receiving various treatments. The complementary value of PET/CT to PSA as a means of gauging treatment response and targeting areas of persistent disease in advanced prostate cancer deserves further study. **Research Support:** This work was supported by U.S. Army Medical Research and Materiel Command grant W81XWH-05-1-0056 (PCRP PC04130).

Other Information:

Presentation Preference: Oral or Poster

Track: Oncology - Clinical Disagnosis

Category: Solid Tumors

Subcategory: Prostate/Genitourinary

FDA Disclosures:

Device/Drug	Fluorine-18 fluoromethylcholine
Status	Investigational

Financial Disclosures:

Sandi Kwee
No Financial Disclosures
Marc Coel

No Financial Disclosures

John Lim

No Financial Disclosures

Print this Abstract

Control Number: 151458

Cancer localization in the prostate by dynamic 18F-choline PET/CT. M. V. Narayanan[*1], S. A. Kwee[2], M. N. Coel[2], J. Lim[2]; 1. Philips Research NA, Briarcliff Manor, NY 2. Hamamatsu/Queen's PET Imaging Center, Honolulu, HI

Objectives: To compare PET/CT kinetic analysis of 18F-choline (FCH) uptake to static PET/CT imaging for sextant localization of primary prostate cancer. **Methods:** Ten patients with ultrasound-guided biopsy localized prostate cancer underwent PET/CT of the prostate after injection of 4 MBq/kg of FCH. List-mode data was reconstructed into dynamic 15-min, static 2-5 min, and static 13-15 min images. Kinetic analysis with an image-derived input function and a 1-tissue compartmental model was used to generate parametric images of k_1, k_2 and distribution volume V_d using Voxulus. Kinetic parameters and static SUV were compared on a prostate sextant basis to the biopsy results. Differences between measures were compared by analysis of area-under-the ROC curve (AUC) and analysis of variance (ANOVA). Voxel-based correlations between parametric and static images were assessed by Spearman's correlation. **Results:** Biopsy detected malignancy in 31/60 sextants. There was no significant difference in AUCs between the kinetic parameters ($k_1^{avg}=0.65$, $k_1^{max}=0.70$, $k_2^{avg}=0.59$ and $V_d^{avg}=0.55$) and static 2-5 min ($SUV^{avg}=0.64$, $SUV^{max}=0.69$) and 13-15 min ($SUV^{avg}=0.73$, $SUV^{max}=0.73$) measures. Voxel-based correlation analysis showed that k_1 parametric images had the highest correlation with the 13-15 min SUV image ($r^{avg}=0.81$), while V_d showed moderate correlation ($r^{avg}=0.66$) and k_2 showed low correlation ($r^{avg}=-0.14$). **Conclusions:** Compartmental modeling of prostatic FCH uptake using an image-derived input function may provide kinetic parameters comparable to static SUV measurement for cancer localization. A slight trend for higher accuracy from static prostate imaging beyond 13 minutes should be weighed against the potential for interference by excreted urinary activity. **Research Support:** 1. Philips Heathcare 2. U.S. Army Medical Research and Material Command grant W81XWH-05-1-0056 (PCRP PC04130).

Supporting Materials:

*figure_attachment.pdf

* Files that are not JPG or GIF will not display on this preview

Other Information:

Presentation Preference: Oral or Poster

Track: Oncology - Clinical Disagnosis

Category: Solid Tumors

Subcategory: Prostate/Genitourinary

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FDA Disclosures:

Device/Drug	fluorine-18 fluoromethylcholine
Status	Investigational

Financial Disclosures:

| Manoj Narayanan	
Position 1	Employee
Company 1	Philips Research North America
Sandi Kwee	
No Financial Disclosures	
Marc Coel	
No Financial Disclosures	
John Lim	
No Financial Disclosures	
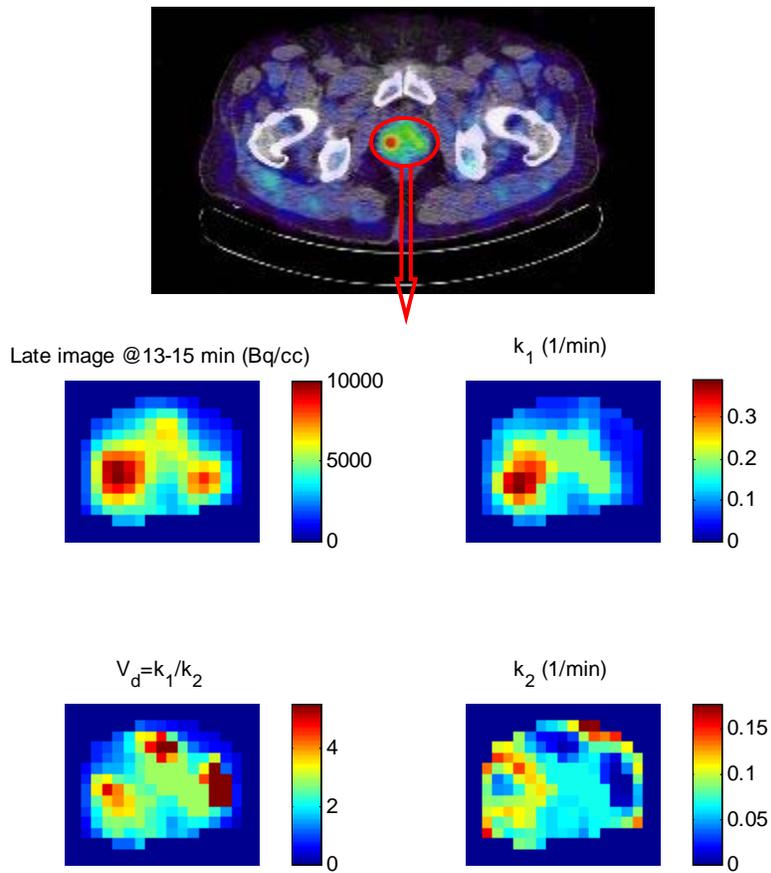
Fig 1: Transverse parametric images of k_1, k_2 and V_d (=k_1/k_2) for a 1-tissue compartmental model are compared to the late time image at 13-15 min post-injection. A fusion image of the CT and late time image is shown on the top indicating the region of interest being analyzed.

APPENDIX 3:

Curriculum Vitae of Principal Investigator

Attached on the next 4 pages

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Sandi Alexander Kwee	Assistant Professor, Univ. Hawaii; Research Director, Hamamatsu/Queen's PET Center.

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Carnegie Mellon University, Pittsburgh, PA	B.S.	1987-1991	Electrical Engineering
University of Pittsburgh, Pittsburgh, PA	M.D.	1992-1996	Medicine
University of Hawaii Residency Program, Honolulu, HI		1996-1999	Internal Medicine
University of Washington, Seattle, WA		2000-2002	Nuclear Medicine/PET

POSITIONS / PROFESSIONAL EXPERIENCE

1988-1991	Computer Programmer, PPG Industries & Department of Economics, Carnegie Mellon University, Pittsburgh, PA
1991-1992	Research Assistant, Neurobehavioral Studies Program, Western Psychiatric Institute and Clinic, Pittsburgh, PA
1996-1999	Internship and Residency, University of Hawaii Internal Medicine Residency Program, Honolulu, HI
1999-2000	Physician, Internal Medicine and Urgent Care, Waianae Coast Comprehensive Health Center, Waianae, HI
1999-present	Medical Staff, The Queen's Medical Center, Honolulu, HI
1999-2000	Medical Staff, Saint Francis Medical Center, Ewa Beach, HI
2000-2002	Fellow, Nuclear Medicine and PET, University of Washington, Seattle, WA
2001-2002	Staff Physician, Emergency Department, Department of Veterans Affairs-Puget Sound Health Care System, Seattle, WA
2001-2003	Medical Officer, Seattle Division- Department of Veterans Affairs, Puget Sound Health Care System, Seattle, WA
2002-2004	Research Fellow, The Queen's Medical Center, Honolulu, HI
2003-2005	Member, Brain Imaging Council, Society of Nuclear Medicine, Term 2003-2005.
2004-2005	Research Associate, The Queen's Medical Center, Honolulu, HI
2004-present	Assistant Professor, Department of Medicine, University of Hawaii John A. Burns School of Medicine, Honolulu, HI
2004-present	Clinical Assistant Professor, Department of Geriatric Medicine, University of Hawaii John A. Burns School of Medicine, Honolulu, HI
2004-present	Member, Cancer Committee, The Queen's Medical Center, Honolulu, HI
2005-present	Research Director, Hamamatsu/Queen's PET Imaging Center, Honolulu, HI
2005-present	Member, University of Hawaii, Cooperative Institutional Review Board (IRB)
2005-present	Associate Member, University of Hawaii Cancer Research Center Clinical Sciences Program

CERTIFICATION

1999	American Board of Internal Medicine
2002	American Board of Nuclear Medicine
2004	Certification Board of Nuclear Cardiology

HONORS AND AWARDS

Research Scholarship in Neuropsychiatry, University of Pittsburgh Medical Center, 1991

Medical Student Research Excellence Award, University of Pittsburgh School of Medicine, 1993.

Scientific Award, Annual Straehley Symposium, Kaiser Foundation, November 1997.

Invited Reader, Japan-US Joint Film Reading Conference. 41st Annual Meeting of the Japanese Society of Nuclear Medicine, October 2001.

Asa Seeds Award (Radiology, Dept. Division of Nuclear Medicine), University of Washington, 2002

RELEVANT PUBLICATIONS

Kwee SA. Coel MN. Lim J. Ko JP. Combined Use of F-18 Fluorocholine PET and Magnetic Resonance Spectroscopy for Brain Tumor Evaluation. Journal of Neuroimaging. 2004 July. 14(3): 285-289.

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Kwee SA, Ko JP, Jiang CS, Watters M, Coel MN. Evaluation of MRI Enhancing Solitary Brain Lesions Using Fluorine-18 Fluorocholine Positron Emission Tomography. Solitary Brain Lesions Enhancing at MR Imaging: Evaluation with Fluorine 18-Fluorocholine PET. Radiology. 2007 Jun 20; PMID: 17581887

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SCIENTIFIC ABSTRACTS (ORAL PRESENTATIONS)

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Kwee S, Lim J, Ko JP, Coel M. *Sextant Localization of Prostate Cancer with F-18 Fluorocholine Positron Emission Tomography.* Scientific Paper Presentation: Prostate Cancer. 51st Annual Meeting. Society of Nuclear Medicine. Philadelphia PA. 2004.

Kwee S. *Fluorine-18 Labeled Choline Derivatives for Brain Tumor PET Imaging.* The Eleventh Conference of Peach through Mind-Brain Science. Research Foundation for Opto-Science and Technology. Ministry of Education, Culture, Sports, Science and Technology, Japan. Shizuoka Prefecture. February 20-22, 2006.

Kwee S, Ko JP, Jiang CS, Watters M, Lim J, Coel MN. *Differentiation Between High-Grade Gliomas and Solitary Brain Metastases: Tumoral and Peritumoral Assessment with Fluorine-18 Fluorocholine Positron Emission Tomography.* Society of Molecular Imaging Annual Meeting, August 2006.

G. Thibault, R. Stack, S. A. Kwee, B. Furusato, M. Coel and I. Sesterhenn. *Initial Results From a Whole Prostate Histopathologic Correlation Study.*, American Urologic Association – Western Section. Annual Meeting. October 2006.

Yun DY, Kwee SA, Wei H, Coel M. *A Surface Adaptive Region Growing Algorithm for Tumor Localization, Object Reconstruction and Shape Visualization*. IEEE 2006 Nuclear Science Symposium and Medical Imaging Conference. October 2006.

Kwee SA, Thibault G, Stack R, Coel M, Furusato B, Sesterhenn I. Non-Invasive Detection and Therapeutic Targeting of Cancer in the Prostate Using Fluorine-18 Fluorocholine Positron Emission Tomography. IMPact 2007, Atlanta, GA.

Kwee SA, Thibault G, Stack R, Coel M, Furusato B, Sesterhenn I. Prostate Imaging with 18F-Fluorocholine Using a Whole-Body Positron Emission Tomograph. Nuclear Science Symposium / Medical Imaging Conference Institute of Electrical and Electronics Engineers 2007.

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Lim J, Kwee S, Cabral C, Turner H, Wakano C, Stokes A, Coel M. *Automated Synthesis and In Vitro Uptake of [18F] Fluoroethylcholine in Prostate Cancer.* Molecular Imaging July-September 2006 5(3).

Kwee S, Ko JP, Jiang CS, Watters M, Lim J, Coel MN. *Fluorine-18 fluorocholine PET Evaluation of Brain Tumor Recurrence Following Radiation Therapy.* Proceedings of the 9th World Congress of Nuclear Medicine and Biology. Seoul, Korea. October 2006.

RESEARCH SUPPORT (PAST 3 YEARS)

Title: Cancer Localization in the Prostate with 18F-Fluorocholine Positron Emission Tomography
Source of Support: Congressionally Directed Medical Research Programs, New Investigator Award PC040130
Dates: 7/2004 – 7/2007
Role: Principal Investigator
Goals: To estimate the accuracy of 18F-fluorocholine PET for intraprostatic cancer localization by correlating the findings of pre-operative PET/CT scanning of the prostate to post-operative whole-prostate histopathology of step-sectioned whole-mount prostate gland specimens obtained from patients with organ-confined prostate cancer treated by radical prostatectomy.

Title: Dynamic PET Study of Prostate Cancer with 18F-Fluorocholine
Source of Support: Philips Medical Systems
Dates: 7/2007 – 7/2008
Role: Principal Investigator
Goals: Evaluate dynamic prostate imaging using time-of-flight PET/CT and retrospective reconstruction of list-mode PET data for detecting malignancy in the prostate gland and pelvic lymph nodes.
Summary of Results: Pilot data on whole-body 18F-choline PET/CT in patients with recurrent prostate cancer was obtained.